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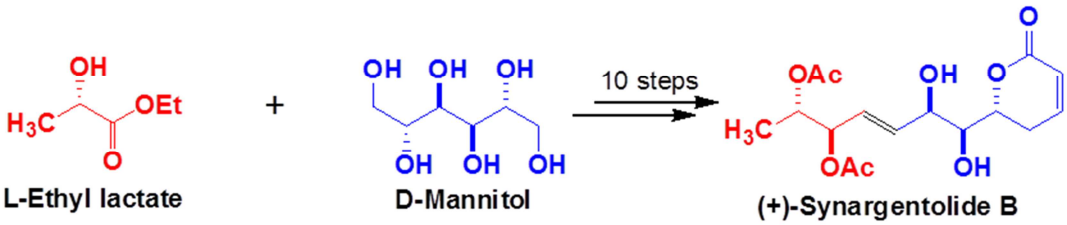

Chiron approach for the total synthesis of (+)-synargentolide B

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A concise and efficient chiron approach for the total synthesis of natural product synargentolide B was achieved in 10 steps with overall yields of 11.3% from D-mannitol and L-ethyl lactate. The key reactions included *anti*-Barbier allylation, cross-metathesis, and an intramolecular Yamaguchi esterification.

1. Introduction

5,6-Dihydro-α-pyrone moiety is an ubiquitous heterocyclic unit found in a number of biologically active natural products, such as synargentolide B (**1**) [1], synargentolide A (**2**), anamarine (**3**),[2] synrotolide (**4**),[3] which have displayed a variety of biological properties, including cytotoxic,[4] antifungal and antibacterial activity[5]. (Figure **1**)

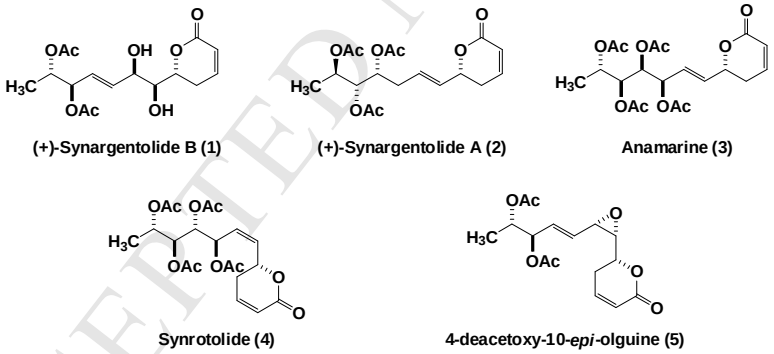


Figure 1. Chemical structures of natural products containing 5,6-Dihydro-α-pyrone

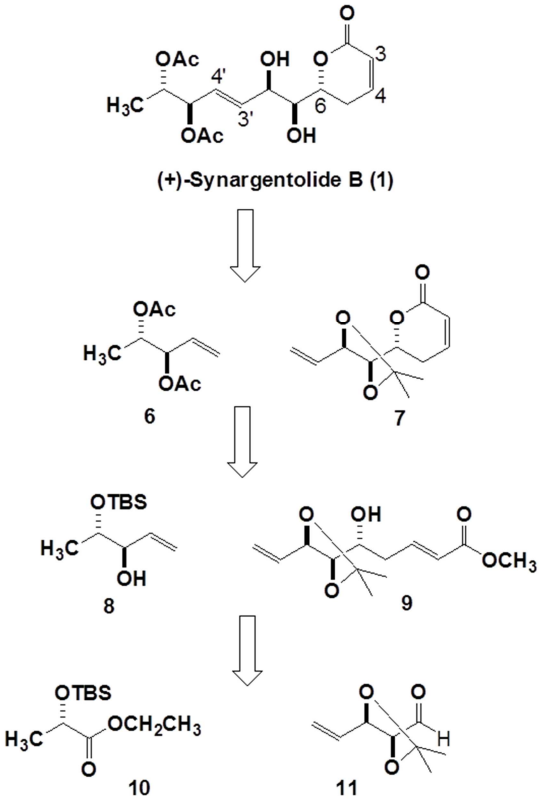
Synargentolide A & B are naturally occurring products consisting of a 5, 6-Dihydro-α-pyrone, free or acetylated 1,2-polyols as well as an unsaturated bond and were first isolated from South African genus *Syncolostemon argenteus* by Rivett et. al in 1998.[1] Initially, the structure of synargentolide B was indecisively established based on extensive spectroscopic analysis.[1] Almost at the same time, the determination of the absolute stereochemistry of synargentolide B was completed by two groups in 2013.[8a,8b] Until now, four total syntheses were reported for (+)-synargentolide B [8] and one synthesis for its analogue[9] in the literature. Prasad et. al[8a] has accomplished the total syntheses of compound **1** and its diastereomers starting from (*S*)-lactic acid and the two enantiomers of tartaric acid using Wittig-Horner

reaction and ring-closing metathesis as their key steps. Meanwhile, Sabitha's work [8b] commenced with D-ribose, D-mannitol, and (+)/(–)-DET to synthesize synargentolide B and its diastereomers through a tandem ring-closing/cross-metathesis reaction.

Herein, we report the synthesis of natural (+)-synargentolide B beginning with D-mannitol and L-ethyl lactate as chiral templates.

2. Results and discussion

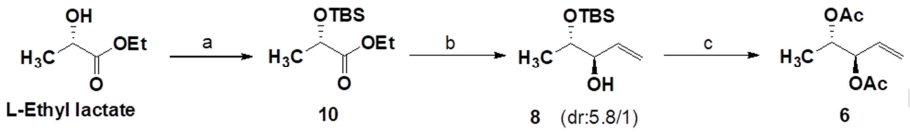
Our approach for the synthesis of (+)-synargentolide B (**1**) is depicted in Scheme **1**. As shown in Scheme **1**, the disconnection process began with two double bonds at C1-C2 and C3'-C4', each of which could be realized by a cross-metathesis reaction and an intramolecular Yamaguchi esterification,[10] respectively. The building block **6** was readily derived from L-ethyl lactate, and the intermediate **7** which contains three contiguous chiral centers could be obtained from commercially available D-mannitol.



Scheme 1. Retrosynthetic analysis of (+)-synargentolide B (**1**)

The synthesis of fragment **6** was accessible from L-ethyl lactate over 4 steps as shown in **Scheme 2**. Protection of L-ethyl lactate as its silyl ether with TBSCl, imidazole in DCM afforded compound **10** in a high yield (96%). Reduction of compound **10** by DIBAL-H in DCM at –78 °C furnished the corresponding aldehyde. Subsequent treatment of the aldehyde generated in situ with vinylmagnesium chloride furnished the desired *anti* product **8** as a 5.8:1 mixture of diastereoisomers.[11] Unfortunately, the attempted separation of the two disasteromers of **8** via flash chromatography proved

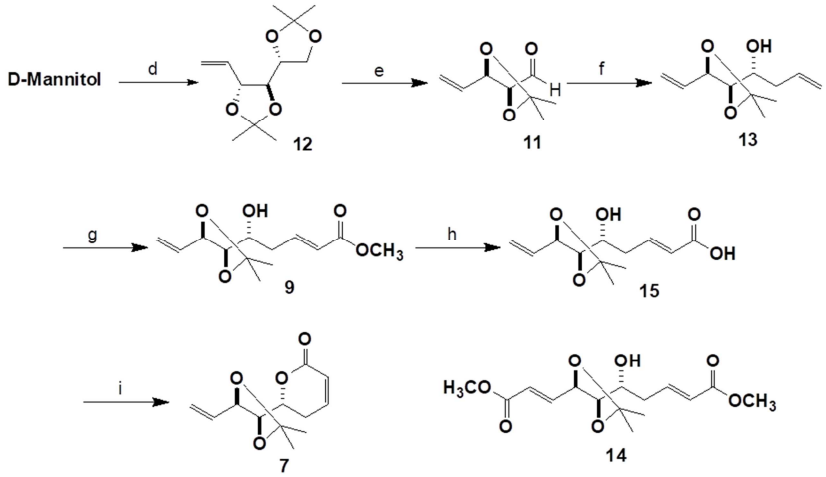
problematic. Deprotection of compound **8** by TBAF in THF followed by peracetylization with acetic anhydride in pyridine provided the building block **6** in 72% yield as a 7:1 separable mixture of C5'-diastereomers.



Scheme 2. Synthesis of compound **6.**

Reagents and conditions: (a) TBSCl, imidazole, DCM, rt, 96%; (b) DIBAL-H, DCM, -78 °C-rt, then vinylmagnesium chloride, Et_2O, -98 °C-rt; (c) TBAF, THF, then Ac_2O, pyridine, 72% for 4 steps.

As depicted in Scheme **3**, our synthesis of compound **7** commenced with D-mannitol, which was converted to **12** in 3 steps in excellent yield according to a modified reported procedure.[12] Selective hydrolysis of primary acetonide and oxidative cleavage of resulting diol occurred simultaneously with H_5IO_6 resulted in **11** in almost quantitative yield. Allylation of the aldehyde **11** under the zinc-mediated Barbier reaction gave homoallyl alcohol **13** as an inseparable anomeric mixture (81%, *anti:syn*=4:1, determined by ^{1}H-NMR). When aldehyde **11** was subjected to the Grignard reaction with allylmagnesium bromide in dry ether, homoallyl alcohol **13** was obtained only in 55% yield as diastereomeric mixture (65:35).

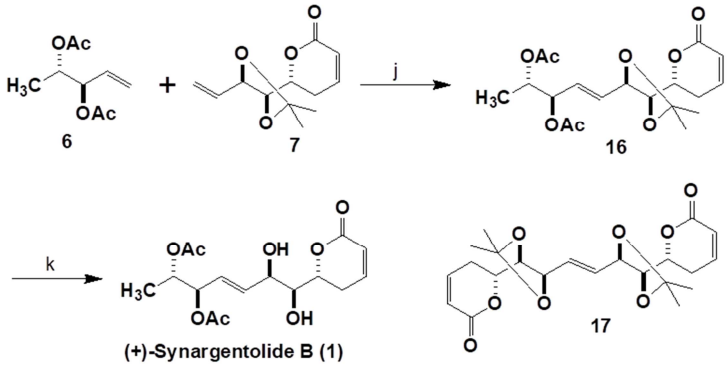


Scheme 3. Synthesis of compound **7.**

Reagents and conditions: (d) ref 12, 69% for 3 steps; (e) H_5IO_6, MeOH, RT; (f) Allyl bromide, excess Zn dust, saturated NH_4Cl, THF, 0-5^{o}C, 72% for 2 steps; (g) methyl acrylate (10 eq), Grubbs' 2nd generation catalyst (0.03eq), DCM, RT,18h, 56%; (h) LiOH, THF, H_2O, RT; (i) 2,4,6-trichlorobenzoyl chloride, pyridine, DCM, 0^{o}C to RT, 83% for 2 steps;

In the next step, we planned to subject diene **13** to mono-cross-metathesis with methyl methacrylate. To ensure selective mono-cross-metathesis of diene, the sterically protecting group acetonide is necessary to be present (Scheme 3). In the case of acetonide protected diene **13**, best results were obtained with 3 mol % of Grubbs' 2nd

generation catalyst in DCM at ambient temperature, 5 equiv of methyl acrylate present from the outset, and slow addition of further 5 equiv over 12h, and the *trans*-α,β-unsaturated ester **9** was obtained in 56% yield with 9% bis-cross-metathesis byproduct **14**.[13] Treatment of ester **9** with LiOH in THF/H_2O afforded the corresponding acid in almost quantitative yield. [10b] Intramolecular esterification of acid **15** under modified Yamaguchi conditions[10] afforded *cis*-α,β-unsaturated lactone **7** in 83% yield as an 8:1 mixture of readily separable diastereomers. The δ-lactonization of **7** could be explained through activation of carboxylic acid with 2,4,6-trichlorobenzoyl and subsequent pyridine assisted addition-elimination.[10b]



Scheme 4. Synthesis of (+)-synargentolide B (**1**).

Reagents and conditions: (j) Grubbs' 2nd generation catalyst (0.05eq), DCM, reflux, 4h, 63%; (k) PPTS, MeOH, reflux, 6h, 78%.

With these two key fragments in hand, we set out to prepare natural (+)-synargentolide B (**1**) through the planned cross-metathesis (Scheme **4**). We are pleased to find that cross-metathesis between side chain **6** and core **7** was successfully carried out by treatment with Grubbs II catalyst in reflux DCM to provide compound **16** in 63% yield with 11% dimer **17**. Finally, removal of the acetonide group in compound **16** by PPTS in MeOH proceeded smoothly to afford (+)-synargentolide B (**1**) in 78% yield.[8] The physical and spectroscopic data (^{1}H and ^{13}C NMR) of our synthetic sample **1** were in good agreement with natural product synargentolide B.[1]

3. Conclusions

In summary, natural (+)-synargentolide B was successfully accomplished by using D-mannitol and L-ethyl lactate as chiral template. Key features of our strategy toward practical total synthesis of (+)-synargentolide B are the efficient combination of a *anti*-Barbier allylation, cross-metathesis, and an intramolecular Yamaguchi esterification. Our convergent and effective strategy provides a candidate for the synthesis of other related synargentolide analogs taking advantage of the inherent chiral centers from natural carbohydrates.

4.Experimental section

4.1 General Experimental

Unless noted otherwise, commercially available materials were used without further

purification. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. All solvents were dried according to the established procedures ahead of use. Flash chromatography (FC) was performed using silica gel (200-300 meshes) according to the standard protocol. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 25 ^{o}C. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer in acetone or methanol as solvent. ^{1}H NMR, ^{13}C NMR were measured on 400 MHz or 100 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform; δ 7.26 for ^{1}H NMR or 77.0 for proton decoupled ^{13}C NMR), and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet and *br* when the signal in question is broadened.

4.2. Experimental Procedures

Synthesis of compound **8**:

To a solution of TBS protected lactate **10**(1.78 g, 7.6 mmol) in DCM (30 mL) was added DIBAL-H (1.2M in toluene, 11.4 mmol) via syringe at -98^{o}C under N_2 protection. After 10 min, vinyl magnesium chloride (21.5mL, 15 mmol) was added into the mixture. The solution was then warmed to room temperature and stirred at room temperature overnight. The reaction was quenched by the addition of saturated K/Na tartrate. The aqueous layer was extracted with DCM. The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude allylic alcohol could be used for next step without any purification. A small sample was purified by flash column chromatography (Hexanes/EtOAc 15:1) to get the physical data of **8** as a 5.8:1 mixture of diastereoisomers: $[\alpha]_D^{25}$ = +27.6 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddd, J = 16.8, 10.8, 6.4 Hz, 1H), 5.28 (dt, J = 17.2, 1.6 Hz, 1H), 5.20 (dd, J = 10.4, 1.6 Hz, 1H), 4.02 (q, J = 2.0 Hz, 1H), 3.86–3.82 (m, 1H), 2.29 (d, J = 4.0 Hz, 1H), 1.07 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.6, 116.5, 71.3, 25.8, 18.1, 17.6, -4.4, -4.9 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{24}O_2SiNa$ $[M + Na]^+$, 239.1443; found 239.1461.

Synthesis of compound **6**:

To a stirred solution of crude **8** (0.85 g, 0.39 mmol) in dry THF (15 mL) was added TBAF (1.31 g, 5 mmol) at room temperature. After completion of the reaction (monitored by TLC), the solution was concentrated under vacuum. The crude diol was used in the next step without further purification. To a vigorously stirred solution of the crude diol in pyridine (8 mL) was added acetic anhydride (1 mL). The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of MeOH (10 mL) and concentrated with toluene. The residue was poured into saturated aqueous $CuSO_4$ (10 mL) and extracted with DCM (3 × 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated

under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 6:1) to give compound **6** as a colorless oil. $[\alpha]_D^{25}$ = -37 (*c* 0.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82-5.71 (m, 1H), 5.33-5.27 (m, 3H), 5.08-5.01 (m, 1H), 2.07 (s, 3H), 2.02 (s, 3H), 1.18 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 170.1, 132.0, 119.4, 75.6, 70.4, 21.1, 21.0, 14.9 ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_9H_{14}O_4Na$ $[M + Na]^+$, 209.0790; found 209.0773.

Synthesis of compound **13**:

To a solution of the diacetonide **12** (150 mg, 0.66 mmol) in EtOAc (10 mL) was added orthoperiodic acid (300 mg, 1.3 mmol) at room temperature and stirred for 30 min. The reaction was quenched by aqueous saturated $NaHCO_3$ (20 mL) and filtered through celite. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic solution was concentrated to give the crude aldehyde **11** as colorless oil. (Caution: The aldehyde **11** was highly unstable and decomposed rapidly on flash column or in $CDCl_3$ at room temperature.) The crude aldehyde obtained could be used in the next step without further purification. To a mixture of crude **11** (ca. 0.66 mmol), Zn dust (86 mg, 1.32 mmol) and allyl bromide (0.114 mL, 13.2 mmol) in THF (8 mL) was added a saturated solution of NH_4Cl (1 mL) by two portions at 0^{o}C. After 15min, the solution was warmed to rt and stirred for further 15min. The mixture was filtered and washed with brine (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 8:1) to give compound **13** (95 mg, 72% over 2 steps) as a mixture of two diastereomers (*anti:syn*=4:1, determined by crude ^{1}H-NMR). $[\alpha]_D^{25}$= +97 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91-5.76 (m, 2H), 5.42 (d, *J* = 17.2 Hz, 1 H), 5.24 (d, *J* = 10.0 Hz, 1H), 5.15-5.10 (m,2H), 4.44 (t, *J* = 7.2 Hz, 1H), 3.86-3.83 (m, 1H), 3.73 (dd, *J* = 8.0,4.4 Hz, 1H), 2.32-2.17 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3,134.0, 118.6, 118.2, 108.9, 82.4, 78.1, 70.3, 37.2, 26.89, 26.86 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C11H18O3Na[M + Na]+ 221.1153; found 221.1178.

Synthesis of compound **9**:

Grubbs 2nd catalyst (15 mg, 0.018 mmol) was added to the mixture of **13** (120 mg, 0.6 mmol) and methyl acrlyate (0.271ml, 3.0 mmol) in dry DCM (15 mL). The reaction was stirred at rt and another 5 equiv of methyl acrylate (0.271ml, 3.0 mmol) was slow added to the solution over 12h. After completion of the reaction (monitored by TLC), the solution was concentrated and purified by flash column chromatography (Hexanes/EtOAc 3:1) to give compound **9** as a yellowish oil (87 mg, 56%). $[\alpha]_D^{25}$ = +74 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03-6.91 (m, 1H), 5.94-5.77 (m, 2H), 5.43 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.0 Hz, 1H), 4.43 (t, *J* = 7.6 Hz, 1H), 3.98-3.94 (m, 1H), 3.74-3.64 (m, 4H), 2.45-2.31 (m, 2 H), 2.26 (*br* s, 1H), 1.43 (s, 3H), 1.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 144.7, 136.2, 123.7,

119.8, 109.2, 82.4, 78.2, 70.0, 51.5, 35.7, 27.1, 26.9 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C13H20O5Na[M + Na]+ 279.1208; found 279.1243.

Synthesis of compound **7**:

To a solution of **9** (44 mg, 0.17 mmol) in THF (5 mL) was added 2M aqueous LiOH (3mL) dropwise and the reaction was stirred for 2 h at room temperature. Amberlite IR-120 (H^+) was then added to neutralize the solution and the mixture was poured into water (10 mL) and extracted with DCM (3 × 10 mL). The combined organic solution was concentrated to give **15** as colorless oil. The crude acid was used in the next step without further purification. To a solution of crude **15** in pyridine (3 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (53mg, 0.20 mmol) in dry DCM (1 mL) at 0^oC and the reaction mixture was warmed to room temperature. After completion of the reaction (monitored by TLC), the solution was concentrated under vacuum. The residue was poured into saturated aqueous $CuSO_4$ (10 mL) and extracted with DCM (2 × 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 2:1) to give compound **7** as a colorless oil (32 mg, 83% for two steps). $[\alpha]_D^{25}$ = +8.1 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (ddd, *J* = 8.8, 5.2, 3.2 Hz, 1 H), 6.03 (dt, *J* = 10.0, 0.4 Hz, 1 H), 5.94 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1 H), 5.45 (d, *J* = 16.8 Hz, 1 H), 5.28 (d, *J* = 10.4 Hz, 1 H), 4.51-4.20 (m, 2 H), 3.92 (t, *J* = 7.2 Hz, 1 H), 2.58-2.53 (m,2 H), 1.45 (s, 3 H), 1.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9, 144.6, 135.3, 121.4, 118.4, 110.0, 80.8, 80.1, 77.8, 27.0, 26.9, 25.9 ppm. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C12H16O4Na[M + Na]+ 247.0946; found 247.0911.

Synthesis of compound **16** and **17**:

To a stirred solution of lactone **7** (72 mg, 0.32mmol) and diacetate 6 (241 mg, 0.072 mmol) in dry CH_2Cl_2 (15 mL) was added Grubbs 2nd catalyst (13 mg, 0.016 mmol) at room temperature. After being stirred under reflux for 4 h, the brown solution was concentrated and purified by flash column chromatography (Hexanes/EtOAc 2:1) to give compound **16** as a colorless oil (77 mg, 63%) and dimer **17** (14 mg, 11%). compound **16**: $[\alpha]_D^{25}$ = +37.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz): δ 6.93 (dt, *J* = 9.6, 4.0 Hz, 1 H), 6.05 (dt, *J* = 9.8, 2.0 Hz, 1 H), 5.88-5.60 (m, 2 H), 5.42 (dd, *J* = 5.2, 4.0 Hz, 1 H), 5.08 (dq, *J* = 6.8, 3.6 Hz, 1 H), 4.43- 4.53 (m, 2 H), 3.90 (t, *J* = 7.2 Hz, 1 H), 2.54-2.57 (m, 2 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.45 (s, 6 H), 1.23 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 170.4, 169.9, 162.6, 144.6, 132.4, 127.3, 121.4, 110.4, 80.9, 79.1, 77.9, 74.5, 70.6, 26.9, 26.2, 21.1, 21.0, 15.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C19H26O8Na: 405.1525, Found 405.1582

compound **17**: $[\alpha]_D^{25}$ -15.8 (*c* 0.3, $CHCl_3$); ^{1}H NMR (400 MHz): δ 6.90 (dt, *J* = 9.6, 4.4 Hz, 2 H), 5.97-6.01(m, 4 H), 4.44-4.50 (m, 4H), 3.94(t, *J* = 7.2Hz, 2 H), 2.54-2.56 (m, 4 H), 1.45 (s, 6H), 1.42 (s, 6H); ^{13}C NMR (100 MHz) δ 162.8, 144.7, 131.2, 121.3, 110.1, 80.5, 79.3, 77.9, 27.0, 26.9, 26.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for C22H28O8Na: 443.1682, Found: 443.1742

Synthesis of (+)-synargentolide B (1):

To a solution of **16** (22 mg, 0.058 mmol) in MeOH (5 mL) was added PTSA.H_2O (4 mg, 0.02 mmol) at room temperature. The mixture was stirred under reflux for 6 h and concentrated under vacuum. The crude was purified by flash column chromatography (Hexanes/EtOAc 1:2) to give synargentolide B (**1**) (15.4 mg, 78%). (+)-Synargentolide B: $[\alpha]_D^{25}$= +39 (*c* 0.45, $CHCl_3$); $[\alpha]_D^{24}$ +25.8 (*c* 1.2, MeOH); $[\alpha]_D^{24}$ +23.3 (*c* 1.2, MeOH) [7a]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (ddd, *J* = 9.2, 4.8, 3.6 Hz, 1H), 6.04 (d, *J* = 9.2 Hz, 1H), 5.89 (dd, *J* = 15.6, 4.8 Hz, 1H), 5.81 (dd, *J* = 15.6, 6.0 Hz, 1H), 5.31-5.34 (m, 1H), 5.06 (dq, *J* = 6.8, 3.6, 1H), 4.48-4.54 (m, 2H), 3.71-3.73 (m, 1H), 2.75(br s, 2H), 2.55-2.57 (m, 2H), 2.09 (s, 3H), 2.05 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 170.2, 163.5, 145.6, 134.1, 127.0, 121.0, 76.8, 75.0, 74.4, 70.6, 69.5, 25.7, 21.3, 21.2, 15.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{22}O_8Na$ $[M+Na]^+$, 365.1212; found 365.1248.

Acknowledgments

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Supporting Information

Supplementary data related to this article can be found at

References

1. Collett LA, Davies-Coleman MT, Rivett DEA. *Phytochemistry* 1998; 48:651-656.
2. Alemany A, Márquez C, Pascual C, Valverde S, Martínez-Ripoll M, Fayos J, Perales A. *Tetrahedron Lett.* 1979; 20: 3583-3586.
3. Coleman MTD, English RB, Rivett DEA. *Phytochemistry* 1987; 26:1497-1499.
4. Hoffmann HMR, Rabe J. *Angew. Chem., Int. Ed.* 1985; 24: 94-110.
5. (a) Larsen AK, Escargueil AE, Skladanowski A, *Pharmacol. Ther.* 2003; 99:167-181; (b) Richetti A, Cavallaro A, Ainis T, Fimiani V, *Immunol. Pharmacol. Immunotoxicol.*, 2003;25:441-449.
6. Pereda-Miranda R, Garcia M, Delgado G. *Phytochemistry.* 1990; 29:2971-2974.
7. Delgado G, Pereda-Miranda R, Romo DA, *Heterocycles.* 1985; 23:1869 -1872.
8. (a) Prasad KR, Gutala P. *J Org Chem.* 2013;78:3313-3322; (b) Sabitha G.; Shankaraiah K, Yadav JS. *Eur J Org Chem.* 2013:4870-4878; (c) Konda, S., Bhaskar K, Nagarapu L, Akkewar DM. *Tetrahedron Lett*. 2014;55:3087-3089; (d) Ramulu U, Rajaram S, Ramesh D, Babu, KS. *Tetrahedron: Asymmetry*. 2015;26: 928-934.
9. Kumaraswamy G, Raghu N, Jayaprakash N, Ankamma K, *Tetrahedron*, 2015;71:5472-5477.

10. (a) Ono M, Zhao XY, Shida Y, Akita H. *Tetrahedron*. 2007; 63:10140-10148; (b) Cai C, Liu J, Du YG, Linhardt, RJ. *J Org Chem.* **2010**;75: 5754-5756.
11. Liu J, Liu Y, Zhang X, Zhang CL, Gao YG, Wang LL, Du YG, *J. Org. Chem.* 2012;77:9718-9723.
12. (a) Yadav VK, Agrawal D. *Chem. Comm.* 2007:5232-5234; (b) Yadav JS, Das S, Mishra AK. *Tetrahedron: Asymmetry*. 2010;21: 2443-2447.
13. (a) Scholl M, Ding S, Lee CW, Grubbs RH. *Org. Lett.*1999;1:953-956. (b) Chatterjee AK, Choi TL, Sanders DP, Grubbs RH. *J Am Chem Soc*. 2003;125: 11360-11370.